Remarks

Claims 1 and 4-20 are pending in the subject application. By this Amendment, Applicants have amended claims 1 and 13 and added new claims 21-24 which are directed to compositions comprising a tissue glue with specific radiotherapeutic agents immobilized therein. Support for the amendments and new claims can be found in the claims as originally filed and throughout the subject specification including, for example, at page 5, lines 5-7, and from page 5, line 28 through to page 9, line 18. Entry and consideration of the amendments and new claims presented herein is respectfully requested. Accordingly, claims 1 and 4-24 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants gratefully acknowledge the Examiner's withdrawal of the Restriction Requirement dated July 26, 2002.

Claims 1 and 4-20 are rejected under 35 USC §103(a) as obvious over Sierra *et al.* (U.S. Patent No. 5,290,552) in view of Matsueda *et al.* (U.S. Patent No. 4,927,916) and Bhargava *et al.* (1989). The Examiner asserts that at the time of the subject invention a person of ordinary skill in the art would have been motivated to combine a composition of Sierra *et al.* as a delivery vehicle for a radiotherapeutic agent as taught by Matsueda *et al.* or Bhargava *et al.* Applicants respectfully traverse this ground of rejection.

Applicants respectfully assert that the cited references, whether taken alone or in combination, do not teach or suggest the claimed invention. The claimed invention is directed to compositions which exert a radiotherapeutic effect on tissue surrounding the site of application of the composition during that time period when the radiotherapeutic agent is immobilized within a tissue glue. An important distinction of the subject invention over the teachings of the cited references is that the radiotherapeutic agent mediates therapeutic activity while it is immobilized in tissue glue. For example, in the case where the radiotherapeutic agent is in particulate form comprising a radioactive isotope, the isotope is not released from the tissue glue so that it may then have a subsequent radiotherapeutic effect. Rather, the particle having the isotope has its therapeutic effect on the region to be treated during that time when the particle is immobilized in the tissue glue. Thus, the present invention provides for very specific localization of radiotherapeutic agents at a particular site or region in need of treatment. This advantageously avoids the unwanted spread of the

radiotherapeutic agent to other areas, which would occur if the agent were released from the tissue glue.

In addressing the remarks submitted in Applicants' Supplemental Preliminary Amendment dated September 26, 2002, the Examiner indicates that Applicants' assertion that the claimed methods do not require the release of the immobilized particle is improper on the grounds that the particles eventually diffuse or absorb. The Examiner concludes that the claimed compositions simply act as an alternative means for "controlled release" of a therapeutic agent. However, Applicants respectfully assert that the claimed compositions are not "controlled release" compositions as suggested by the Examiner and do not function as a means for the "controlled release" of a therapeutic agent.

The specification clearly teaches the claimed compositions formulated to avoid the release of active radiotherapeutics. In addition, in a sincere effort to expedite prosecution of the subject application to completion, claim 1 has been amended to recite that the radiotherapeutic agents are immobilized in the tissue glue for a sufficient amount of time to exert a radiotherapeutic effect. The radioactivity of the agents will decrease over time, at a rate depending upon the half-life of the isotope of the particular radiotherapeutic agent. As indicated at page 9, lines 10-18, of the subject specification:

> "Because the radioactivity is incorporated in a substance which does not diffuse through tissue glue, the application of tissue glue to the injection site will prevent leakage. The half-life of the ^{90}Y is sufficiently short that most of the radioactivity will have decayed before the tissue glue will have broken down. In this aspect, the invention provides a system which inhibits unwanted spread of synovectomy agent." (emphasis added)

The specification teaches that the tissue glue is formulated to remain stable and, thus, the radiotherapeutic agents are immobilized for a sufficient amount of time for the radioactivity of the radiotherapeutic agent to decay to a point such that there is only minimal radioactivity. The radiotherapy is localized in the area immediately surrounding the tissue glue. It is only once the radioactivity has decayed substantially that the tissue glue starts to break down, releasing the radiotherapeutic agent from the glue. At the time of such release, the radiotherapeutic agents have

only minimal radiotherapeutic activity. The claimed compositions therefore allow for short distance radiotherapy, such as brachytherapy, which gives a high radiation dose to a tumor while reducing the radiation exposure in the surrounding healthy tissues. The subject specification at page 17, lines 25-30, indicates:

> "In another aspect where tissue glue is used to hold a ^{103}Pd ferrite for brachytherapy, the half-life of the nuclide requires a relatively long period of stability of the gel in order to minimize the spread from the site of application prior to the passage of three to five half-lives."

Accordingly, there is no requirement that the radiotherapeutic agents of the claimed invention be released from the tissue glue in order for the agents to have a radiotherapeutic effect, and such a release is contrary to the teachings in the subject specification. The claimed compositions comprise agents which exert a radiotherapeutic effect while they are immobilized in the tissue glue. That is, the immobilized radiotherapeutic particles emit radioactivity, for example in the form of β-particles, which passes through the glue and has a radiotherapeutic effect on the immediately surrounding tissue.

The retention of the radiotherapeutic agent in tissue glue in order for the radiotherapeutic agent to have the desired effect on the targeted tissue is not taught or suggested by any of the references cited by the Examiner. There is no teaching or suggestion in any of the references cited by the Examiner that a composition comprising a radiotherapeutic agent within a tissue glue can be used to provide a therapeutic effect while the radiotherapeutic agent is immobilized in the glue. Applicants respectfully assert that a fair reading of the cited references leads an ordinarily skilled artisan to conclude that, in order for therapy to occur, the therapeutic agent must actually leave the tissue glue and move to the surrounding tissue. Moreover, Applicants submit that the compositions described in the cited references are not capable of exerting their primary therapeutic effect while immobilized in a tissue glue.

The Sierra *et al.* patent, the primary reference relied upon by the Examiner under this rejection, describes a surgical adhesive material comprising fibrinogen, Factor XIII, collagen, thrombin, Ca^{2+}, and, optionally, an antifibrinolytic agent (see the Abstract of the Sierra *et al.* patent).

The compositions described in the Sierra *et al.* patent may act as a vehicle for therapeutically active substances, in particular, growth factors, cytokines or immunoglobulins and metabolic substances (see column 4, lines 63-66, and column 5, lines 7-15, of the Sierra *et al.* patent). It is stated in the Sierra *et al.* patent at column 5, lines 3-6, that such substances would "serve to recruit or expand the leukocyte or endothelial population, inhibit pathways of leukocytes, endothelial cells or the like, or impact novel peptides." It is clear from the disclosure therein, the Sierra *et al.* patent contemplates that any therapeutically active substances encompassed in the adhesive material must be released from the adhesive material in order to have any such therapeutic effect. The adhesive material of Sierra *et al.* therefore functions as a vehicle to deliver and release therapeutic substances. There is no teaching or suggestion in the Sierra *et al.* patent that such adhesive compositions could have any therapeutic activity or beneficial function before the release of the therapeutically active substance from the adhesive material occurs. Moreover, there is no teaching or suggestion in Sierra *et al.* of adhesive compositions that comprise a therapeutic agent which is capable of exerting a therapeutic effect while the agent is immobilized in the adhesive. Indeed, the existence of therapeutic activity while the agent is immobilized, rather than following release from the adhesive material, would be contrary to the purpose of a controlled release vehicle. Accordingly, Applicants respectfully assert that the Sierra *et al.* patent actually teaches away from the present invention in that the adhesive material releases therapeutic substances into the surrounding environment so that substances can then provide their therapeutic effect subsequent to their release. A reference that teaches away from an invention is a *per se* demonstration of a lack of *prima facie* obviousness since teaching away is the opposite of suggesting the invention. *In re Dow Chemical Co.*, 5USPQ2d 1529 (Fed. Cir. 1988). There can be no therapeutic effect until the therapeutic agent is released from the adhesive material of Sierra *et al.*

As the Examiner has acknowledged in the instant Office Action, the Sierra *et al.* patent does not disclose or suggest the inclusion of any radiotherapeutic agent in the adhesive material. There is no teaching or suggestion that the adhesive material might comprise any component capable of exerting a radiotherapeutic effect while immobilized in the adhesive. In fact, the therapeutic agents referred to in Sierra *et al.* are of a wholly different type of agent than is used in the claimed invention and are entirely unrelated to radiotherapy. The Examiner relies on the Matsueda *et al.* patent and the

Bhargava *et al.* reference as teaching a radiotherapeutic agent in an attempt to cure this deficiency of the Sierra *et al.* patent.

The Matsueda *et al.* patent and the Bhargava *et al.* reference both describe radiolabeled antibodies. The Matsueda *et al.* patent is concerned with the use of radionuclides only for labeling antibodies for detection, not for any therapeutic effect. Although the Bhargava *et al.* reference does mention that radiolabeled antibodies may be used for therapeutic purposes, the focus of the reference is clearly on methods for radiolabeling antibodies, and not on the use of radiolabeled antibodies for therapy.

Even assuming that the Matsueda *et al.* patent and the Bhargava *et al.* reference taught radiolabeled antibodies for therapeutic use, it is clear that the antibodies described in the Matsueda *et al.* patent and the Bhargava *et al.* reference must be released into the surrounding biological environment in order for the antibodies to bind their targets and have a therapeutic effect. There is no teaching or suggestion in either reference that the antibodies described therein exert any kind of therapy for their target site while they are immobilized in a glue or adhesive. The whole point of using an antibody for therapy is because antibodies can be produced that will bind to a specific antigen on a cell. It would be incongruous to use a radiolabeled antibody to try to effect radiotherapy in a subject by using a delivery vehicle that did not release the antibody until after radioactivity of the radiolabel had substantially decayed and thereby prevented the antibody from binding to its target antigen while the antibody was radiotherapeutically active.

Motivation

Applicants respectfully assert that at the time of their invention, the ordinarily skilled artisan would not have had any incentive or motivation to combine the teaching of the Sierra *et al.* patent with that of the Matsueda *et al.* patent or the Bhargava *et al.* reference. As noted above, the Matsueda *et al.* patent and Bhargava *et al.* reference provide radiolabeled antibodies that must bind to specific targets in order to have a therapeutic effect. There would be no motivation for the ordinarily skilled artisan to include such components in a tissue glue of the claimed invention because, as noted above, the claimed compositions are formulated to retain the therapeutic agent until such time a substantial level of radioactivity has decayed. Release of radiolabeled antibodies after such time as their radioactivity has decayed is contrary to the intended therapeutic function and use of such antibodies.

Even if a person of ordinary skill in the art were to combine the teaching of either Matsueda *et al.* or Bhargava *et al.* with that of Sierra *et al.*, they would not arrive at a composition according to the present invention: A combination of the cited references would not lead the ordinarily skilled artisan to include a radiotherapeutic agent in a tissue glue formulation. In particular, such a combination would not lead the skilled person to produce a composition comprising a tissue glue and a radiotherapeutic agent, wherein the agent is immobilized in the glue for a period of time sufficient for a radiotherapeutic effect. The compositions described in the cited references contain a different type of therapeutic agent and operate in a different way from that of the claimed invention.

Accordingly, Applicants respectfully assert that the claimed compositions and methods would not have been obvious over the combination of references cited in the outstanding Office Action. In particular, the Sierra *et al.* patent, in view of Matsueda *et al.* and Bhargava *et al.*, does not provide the ordinarily skilled artisan considering these references with any incentive or motivation to develop compositions wherein a radiotherapeutic agent is immobilized in a tissue glue for a period of time sufficient for a radiotherapeutic effect and, in fact, the cited references teach away from the claimed invention.

In regard to new claims 21-24, Applicants respectfully assert that there is no teaching or suggestion in any of the Sierra *et al.*, Matsueda *et al.*, or Bhargava *et al.* references to produce compositions including as a radiotherapeutic a composition comprising a ferrite, and even less suggestion of a β-emitting ferrite, a zinc substituted yttrium ferrite or a ^{56}Fe-enriched ferrite, or a ferrite comprising the specific radionuclides ^{103}Pd or ^{90}Y. There is also no teaching which would lead the skilled person to such compositions.

Applicants respectfully assert that the claimed invention is not obvious over the cited references, regardless of whether the references are taken alone or in combination. As the Examiner is undoubtedly aware, it is well established in patent law that in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicants respectfully assert that one finds neither the teaching or suggestion of the claimed invention, nor a reasonable expectation of success for obtaining it, in the references cited in the

outstanding Office Action. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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DRP/sl
Attachment: Marked-Up Version of Amended Claims

Marked-Up Version of Amended Claims

Claim 1 (twice amended):

1. A composition comprising a tissue glue and, immobilized in the glue, in particulate form, a radiotherapeutic agent or an agent convertible to a radiotherapeutic, [whose therapeutic effect is mediated locally, when immobilized in the glue] wherein the agent is immobilized in the glue for a period of time sufficient for a radiotherapeutic effect.

Claim 13 (twice amended):

13. [A] The composition according to claim 1, further comprising an antibody, and wherein the tissue glue is a fibrinogen tissue glue.